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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/654,276	09/01/2000	Smadar Cohen	9124.117US01	5848

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/654,276	COHEN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9,10 and 16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9,10 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/12/04 has been entered. Applicant's amendment filed on 11/12/04 has also been entered. Claims 1-3, 5-6, 9-10, and 16-24 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in the previous office action.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1-3, 5-6, 9-10, and 16-24 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn in view of applicant's amendments to the claims and arguments. Specifically, the applicant has amended the claims so that they are limited to the transplantation of fetal, autologous, or allogeneic cardiomyocytes either alone or in combination with fetal, autologous, or allogeneic endothelial cells, fibroblasts, or smooth muscle cells. In

regards to the transplantation of allogeneic cells, applicant's arguments concerning the state of the art of allogeneic transplantation at the time of filing have been found persuasive.

The following are new grounds of rejection, not necessitated by applicant's amendments. As such, this office actions is non-final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-6, 9-10, and 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,099,832 (8/8/00), hereafter referred to as Mickle et al., in view of WO 97/44070 (11/27/97), hereafter referred to as Shapiro et al.

It is noted that these references were previously included in a 103 rejection applied to claim 1-3 that was withdrawn by the examiner in the office action mailed on 10/21/02. However upon further consideration, the examiner has determined that these two references by themselves apply to all pending claims 1-3, 5-6, 9-10, and 16-24.

The applicant claims methods of preparing a three-dimensional tissue-engineered biograft comprising co-culturing a porous polysaccharide matrix comprising polymeric microspheres capable of releasing soluble angiogenic growth factors with fetal, autologous, or allogeneic cardiomyocytes either alone or in combination with fetal, autologous, or allogeneic endothelial cells, fibroblasts, or smooth muscle cells, until a cardiac-like tissue is formed. The applicant further claims the three-dimensional tissue-engineered biograft made using said method, and methods of repairing a damaged myocardium comprising transplanting said tissue-engineered biograft onto myocardial tissue or myocardial scar tissue. In addition, the applicant claims said methods and products wherein the polysaccharide matrix comprises an alginate polysaccharide.

Mickle et al. teaches methods of treating defective, damaged, or scarified heart tissue comprising transplanting onto the defective, damaged, or scarified heart tissue, a therapeutic graft comprising a biodegradable scaffold supporting cells comprising a combination of adult or pediatric cardiomyocytes and endothelial cells (Mickle et al., claims 9-19, and columns 5-6). Mickle et al. further teaches that the therapeutic graft comprises growth factors including soluble angiogenic growth factors such as FGF or VEGF (Mickle et al., claims 17-18). In addition, Mickle et al. teaches that the cells for transplantation are autologous or allogeneic (Mickle et al, column 2).

Mickle et al. differs from the instant invention by teaching the use of biodegradable scaffolds made of collagen rather than alginate polysaccharides. Mickle et al. further differs by not specifically teaching that the soluble growth factors are contained in polymeric microspheres. Shapiro et al. supplements Mickle et al. by teaching the use of alginate polysaccharide as scaffolds for cells transplantation (Shapiro et al., page 5). Specifically, Shapiro et al. teaches methods of therapeutic autologous or allogeneic cell transplantation where the cells to be transplanted are first grown in vitro on or within the alginate polysaccharide matrix until they reach a desired state of differentiation and then transplanted into the patient at a desired site for the purpose of tissue repair or replacement (Shapiro et al., paragraph 2). Shapiro et al. further provides motivation for using the alginate polysaccharide matrix over other biodegradable matrixes, such as collagen, by teaching that collagen-based matrices used as cell transplantation matrixes have several disadvantages including the contraction of the collagen scaffold during in vitro culture which makes this scaffold unsuitable for prolonged in vitro cultivation of cells, and a rapid rate of degradation in vivo (Shapiro et al., page 3). Shapiro et al. states that because of the drawbacks of using collagen in matrixes for transplantation, polysaccharide polymer scaffolds are preferred because they support the growth of thick layers of cells and are capable of maintaining the cells in an active functional state before and after implantation/transplantation in a host tissue, and are further amendable to vascularization (Shapiro et al., page 5). Shapiro et al. further supplements Mickle et al. by teaching that it is advantageous to include growth factors, particularly angiogenic growth factors, in the polysaccharide matrix in order to encourage more rapid growth of the cells on the matrix and to encourage vascularization of the implant in a host, and that since growth factors are usually too small to be effectively retained within the

polysaccharide matrix, they should be incorporated in the matrix in the form of controlled release microcapsules (Mickle et al., page 11).

Therefore, in view of the substantial benefits to using alginate scaffolds over collagen scaffolds taught by Shapiro et al., it would have been *prima facie* obvious to the skilled artisan to substitute the alginate scaffolds containing controlled release microcapsules containing growth factors taught by Shapiro et al. for the collagen scaffolds containing soluble growth factors taught by Mickle et al. in the methods of treating damaged cardiac tissue taught by Mickle et al. Further, based on the successful growth of cells in the alginate matrix taught by Shapiro and the successful treatment of damaged myocardium by transplanting cardiomyocytes taught by Mickle et al., the skilled artisan would have had a reasonable expectation of success in treating damaged myocardium by transplanting an alginate polysaccharide matrix containing autologous or allogeneic cardiomyocytes to the site of myocardial damage.

For the purpose of compact prosecution, applicant's previous arguments concerning the teachings of Mickle et al. and Shapiro et al. are addressed in so far as they pertain to the instant grounds of rejection.

The applicant previously argued that Mickle does not teach the use of a polysaccharide matrix, and that Shapiro does not teach co-culturing any of the cells types recited in the instant claims in the polysaccharide matrix or treat treating damaged myocardium. In response, the rejection of record acknowledges that Mickle et al. does not teach the polysaccharide matrix, however, Shapiro et al. been cited not only for teaching the polysaccharide matrix, but also for providing specific motivation for using a polysaccharide matrix over the collagen matrix taught

by Mickle et al. as a support to grow cells in vitro and to use as a therapeutic graft in vivo to treat damaged tissue. Since Mickle et al. already teaches the treatment of damaged myocardium using cardiomyocytes and endothelial cells grown on a biodegradable matrix and provides a reasonable expectation of success for such treatment, Shapiro et al. has only been cited to provide motivation to use a polysaccharide matrix over the collagen matrix taught by Mickle. Shapiro et al. provides ample motivation for this substitution by teaching the disadvantages of using collagen scaffolds and the advantages of using polysaccharide scaffolds (see above, and Shapiro et al., pages 3 and 5). Thus, the rejection of record details how the combination of Mickle et al. and Shapiro teach all the limitations of the claims as written, provides specific motivation for combining the teachings of Mickle et al. and Shapiro et al., and explains why the combination of the two references provides a reasonable expectation of success. As such, the office has met the burden for establishing a *prima facie* case of obviousness.

Specification

The abstract of the disclosure is objected to because it is in the form of a claim and contains legal phraseology. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. **The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided.** The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER